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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/542,839	12/13/2005	Tetsuo Kojima	14875-148US1 C1-A0231P-US	8994
26161	7590	03/17/2010	EXAMINER	
FISH & RICHARDSON PC P.O. BOX 1022 MINNEAPOLIS, MN 55440-1022			BRISTOL, LYNN ANNE	
			ART UNIT	PAPER NUMBER
			1643	
			NOTIFICATION DATE	DELIVERY MODE
			03/17/2010	ELECTRONIC

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/542,839	<b>Applicant(s)</b> KOJIMA, TETSUO	
	<b>Examiner</b> LYNN BRISTOL	<b>Art Unit</b> 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 12/2/09 and 1/6/10.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1,2,4-7,10,14,15,18 and 27-32 is/are pending in the application.
- 4a) Of the above claim(s) 10 and 18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,2,4-7, 14, 15 and 27-32 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                       | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____                                      |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>2/3/10</u> .  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

1. Claims 1, 2, 4-7, 10, 14, 15, 18, and 27-32 are all the pending claims for this application.
2. Claims 1, 2, 6, and 7 were amended, Claims 3, 13, and 19-26 were cancelled and new Claims 27-32 were added in the Response of 12/2/09.
3. Claims 1, 2, 6, 7, 27, 28, 31 and 32 were amended in the Response of 1/6/10.
4. Claims 10 and 18 are withdrawn from examination.
5. Claims 1, 2, 4-7, 14, 15 and 27-32 are all the pending claims under examination.
6. Applicants amendments to the claims have necessitated new grounds for objection and rejection. This Office Action is final.

### ***Information Disclosure Statement***

7. The IDS of 2/3/10 has been considered and entered. The initialed and signed 1449 form is attached.

### **Rejections Maintained**

#### ***Claim Rejections - 35 USC § 112, first paragraph***

#### ***Enablement***

8. The rejection of Claims 1, 2, 4-7, 15 and 27-32 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained.

The rejection was set forth in the Office Action of 6/20/08 as follows:

#### **"Nature of the Invention/ Skill in the Art**

Claims 1 and 3-6 are interpreted as being drawn to a method of screening for commonly shared antibody light chains which correspond to two or more types of different antibody heavy chains where in the initial step host

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cells "secreting" the heavy chain against a target antigen are provided, then a phage library encoding a plurality of different light chains is introduced into the host cells in order to secrete a library of phage particles presenting the heavy chain and a light chain, where the library is screened for specific binding to the target antigen, then where the screened library is introduced into host cells "secreting" a second heavy chain that binds to a different antigen than the first antigen in order to secrete a library of phage particles presenting the second heavy chain and a light chain, and finally where the phage libraries produced from the second introducing step are selected for binding to the second target antigen (Claim 1), where the first and second heavy chains are Fd (Claim 3), the host is E. coli (Claim 4), the steps are performed twice or more (Claim 5) and the method further comprises introducing the second screened phage particle library into a host "secreting" a third heavy chain that binds to a third and different antigen from the first and second antigens and selecting the phage particle library that bind to the third antigen (Claim 6).

Claims 2, 7 and 13-15 are interpreted as being drawn to a method of screening for commonly shared antibody light chains which correspond to two or more antibody heavy chains of different amino acid sequence where in the initial step host cells "secreting" the heavy chain against a target antigen are provided, then a phage library encoding a plurality of different light chains is introduced into the host cells in order to secrete a library of phage particles presenting the heavy chain and a light chain, where the library is screened for specific binding to the target antigen, then where the screened library is introduced into host cells "secreting" a second heavy chain comprising a different amino acid sequence than the first heavy chain in order to secrete a library of phage particles presenting the second heavy chain and a light chain, and finally where the phage libraries produced from the second introducing step are selected for binding to the target antigen recognized by the second antibody (Claim 2), and the method further comprises introducing the second screened phage particle library into a host "secreting" a third heavy chain having an amino acid sequence different from the first and second heavy chain and selecting the phage particle library that bind to the antigen recognized by the third heavy chain (Claim 7), where the first and second heavy chains are Fd (Claim 13), the host is E. coli (Claim 14), and the steps are performed twice or more (Claim 15).

The relative skill in the art required to practice the invention is a molecular immunologist with a background in phage display library production and screening for recombinant antibodies.

#### Disclosure in the Specification

The specification generally teaches methods of screening for commonly shared light chains which correspond to two or more types of different antibody heavy chains. Hosts which secrete heavy chains of antibodies that bind to desired antigens must be obtained first. Two types of hosts that each secretes a heavy chain corresponding to one of the two types of desired antigens are necessary for generating a BsAb, three types are necessary for a tri-specific antibody, and four types are necessary for a tetra-specific antibody. To obtain these hosts, the specification teaches producing antibody-producing cells from mammals (p. 7, lines 9-28). Host cells that secrete antibody heavy chains may secrete full-length antibody heavy chains or partial fragments (p. 10, lines 21-23). A gene portion that encodes a desired antibody heavy chain is introduced into an expression vector that is suitable for expression in appropriate host cells. Host cells are preferably bacteria that can be infected by phages, particularly gram negative bacteria (p. 10, lines 30-35). Phage particles contemplated by the invention are listed on p. 12, lines 20-23.

The following examples are provided for performing method steps:

Eukaryotic host cell/ expression vector (working example): the specification at p. 13, lines 2-16 incorporates by reference the disclosure from WO 95/15393 for constructing antibody libraries using eukaryotic cells that present antibodies on their cell surfaces. An expression vector carrying a gene that encodes a desired heavy chain (for example, Fd), and is linked downstream of a promoter appropriate for its expression and a signal sequence which enables the secretion of the heavy chain, is introduced into eukaryotic host cells. Expression vectors are constructed with light chain-encoding genes linked to a transmembrane region-encoding sequence and inserted downstream of an appropriate promoter, so that the light chains will be displayed on cell surfaces when expressed. By introducing light chain expression vectors into the aforementioned heavy chain-secreting host cells, host cells which *express on their cell surfaces* antibodies that bind to a desired antigen can be selected. The displayed antibody is a Fab fragment when Fd is used as the heavy chain and those comprising VL and CL are used as the light chains.

Bacterial host cell/ phage library (prophetic example): A light chain library is introduced into the E. coli host which expresses an antibody A heavy chain (for example, Fd), and by infecting the host with helper phages, a phage library, which presents *on their surfaces* antibodies comprising an antibody A heavy chain and various light chains (Fab when the heavy chain is Fd and the light chain comprises VL and CL) as fusion proteins (p. 12, line 30- p. 13, line 1).

The specification is enabling for using a host cell system compatible with a phage library being introduced into the host cell such as a bacterium which produces phage particles expressing an assembled antibody heavy and light chain on the particle surface after following the method steps. The specification is not enabling for introducing a phage library into just any host cell much less where the host cell is a eukaryotic cell. The specification is not enabling for any host cell having the ability to "secrete" an antibody heavy chain much less where a bacterial host cell secretes the first or second or third antibody heavy chain. The claims encompass any host cell a) having the ability to secrete

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an antibody heavy chain and b) capable of being infected with a phage particle library whereas the specification is only enabling for using phage particles to infect a bacterium where at most the resultant, selected phage particle library also expresses the heavy chain and light on the surface. The specification is not enabling for the genus of host cells having all of the properties of the instant claimed method.

Prior Art Status: E. coli host cells express and transport antibody fragments comprising a bacterial signal peptide into the periplasmic space

The prior art does not recognize bacterial cells, more specifically E. coli, as being capable of secreting antibody fragments absent the fragment being engineered to have a bacterial signal peptide. As reviewed by Kipriyanov et al. (Molec. Biol. 12: pp. 173-201 (1999)) E. coli can express antibody fragments such as Fab, Fv and scFv into the periplasm. "Periplasmic expression has permitted the functional testing of a wide variety of antibody fragments with different antigen binding specificities. The antibody fragments are usually correctly processed in the periplasm, they contain intramolecular disulfide bonds and are soluble. However, the high-level expression of a recombinant protein with a bacterial signal sequence in E.coli often results in the accumulation of insoluble antibody fragments after transport to the periplasm, presumably via the aggregation of a folding intermediate"...and "high protein concentrations of the secreted antibody fragment in the periplasmic space would favor the formation of insoluble aggregates over correct folding."

Thus one of skill in the art could not even predict that any antibody heavy chain could be "secreted" by any host cell much less a bacterium and that the same host cell could be infected with a library of phage particles encoding any random antibody light chain where the host cell then produced a phage particle expressing on its cell surface an assembled heavy and light chain antibody with specific antigen binding ability or at least antigen binding ability for the recognized antigen of the heavy chain. Because of the lack of working examples in the specification for the scope of host cells encompassed by the instant method claims, the ordinary artisan would be forced into undue trial and error experimentation to practice using the method based on the written description in the specification alone."

### The rejection was maintained in the Office Action of 6/3/09 as follows:

"Applicants allegations on pp. 8-11 of the Response of 3/17/09 have been considered and are persuasive in part as regards point (1) (a phage library in any kind of host cell) on p. 9 but unpersuasive as regards point (2) (making the method work in bacterial cells) on p. 9.

As regards *point (1)*, Applicants allege that in amending the generic claims to require that the host is bacterial in order to be infected with a phage library, point one (1) of the rejection is overcome. The examiner concurs that this aspect of the rejection is overcome.

As regards *point (2)*, Applicants allege "the observation that recombinant proteins in E. coli can aggregate when expressed at high levels is largely irrelevant to a screening method, in which high level expression of individual library members is not needed. Use of phage libraries in bacterial hosts to screen for two-chain antibodies is well known in the art, so techniques for avoiding aggregation of the secreted chain--if it is ever an issue--are apparently known. See, for example, Griffiths et al., The EMBO Journal 13:3245-3260 (1994)"; Kipryanov recognized that these methods work; and "The fact that, as Kipryanov goes on to note, high level expression of a recombinant protein in E. coli (e.g., for large-scale production of a desired antibody) may result in aggregation is irrelevant to the question of whether lower levels that are adequate for screening purposes would work."

#### Response to Arguments

Applicants have not even provided a copy of the Griffiths reference with their filed Response of 3/17/09 thus precluding the examiner from verifying the reference content.

As regards the examiner's previous reference to Kipryanov, it is noted that Applicants have conveniently edited the reference interpretation in favor of their position, which is to wholly ignore it's teaching, namely, that in order for this method to work in a bacterium, where the bacterial host cells are "secreting the heavy chain of an antibody" as instantly claimed, the protein would be required to comprise a bacterial signal peptide in order to even be expressed in the periplasmic space much less "secreted." Elements (a) and (d) in each of the generic claims 1 and 2 require protein secretion from a bacterial host.

As regards Applicants assertion that screening antibodies does not require the same extent of expressed protein as required for large-scale production, the examiner finds this to be wholly irrelevant to the instant rejection. Zauderer et al. (US 20080167193; published 7/10/08; priority to 11/14/01) substantiate the examiner's position stating:

"Immunoglobulin libraries constructed in bacteriophage may derive from antibody producing cells of naive or specifically immunized individuals and could, in principle, include new and diverse pairings of human immunoglobulin heavy and light chains. Although this strategy does not suffer from an intrinsic repertoire limitation, it requires that

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complementarity determining regions (CDRs) of the expressed immunoglobulin fragment be synthesized and fold properly in bacterial cells. Many antigen binding regions, however, are difficult to assemble correctly as a fusion protein in bacterial cells. In addition, the protein will not undergo normal eukaryotic post-translational modifications. As a result, this method imposes a different selective filter on the antibody specificities that can be obtained" [0013],

and

"Assays for expression in bacterial hosts are often impeded, however, because the protein may not be sufficiently expressed in bacterial hosts, it may be expressed in the wrong conformation, and it may not be processed, and/or transported as it would in a eukaryotic system. Many of these problems have been encountered in attempts to produce immunoglobulin molecules in bacterial hosts..." [0016]."

Applicants allegations on pp. 9-12 of the Response of 12/2/09 and further in view of the amendments to the claims have been considered and are not found persuasive.

Applicants allege the invention involves phage-based antibody screening assays that involves association of separate heavy and light chains (or fragments thereof) on the surface of the phage generally require that both of the chains be secreted in the periplasmic space (one of the chains being fused to a phage protein that self-assembles with other phage proteins to form the phage particle and the second chain being expressed as a separate polypeptide that associates with the phage- anchored chain). This is illustrated by the Griffiths et al. reference (EMBO J 13:3245-3260)."

#### Response to Arguments

The examiner has considered the arguments, the Griffiths reference and the amended claims in combination and does not find the method as being enabled for its intended use based on the claim amendments. Looking to the specification for what is actually disclosed and enabled and in view of the cited art references, the examiner concludes that the claims recite elements that are not supported by the specification that would permit an operable method.

For example, the specification only teaches the following:

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“[0062] Generally, to generate a phage library, light chain-encoding DNAs are incorporated into appropriate phage vectors, so that the light chains will be displayed on the external surface of the phages, as fusion proteins with coat proteins or display anchor proteins. Herein, there are no particular limitations on the phage vectors. Generally, they are vectors that contain a bacteriophage replication origin (ori), and are induced through modifications of the phage genome. Phage vectors preferably encode, in the direction from N to C terminus, (1) a light chain, and (2) a phage membrane anchor domain (all or a portion of a coat protein or display anchor protein). Furthermore, a sequence encoding the prokaryotic cell secretion signal domain, which enables proteins encoded by the above-mentioned (1) and (2) to be secreted to the outside of host bacterial cells and incorporated into bacteriophages, is placed before the sequence encoding the light chain of (1), as necessary”,

and

“[0068] WO95/15393 also proposes construction of antibody libraries using eukaryotic cells, which allows more accurate investigation of the actual antigen-binding capacity of antibodies from the screening stage. Therefore, in place of bacterial hosts such as E. coli, the methods of the present invention can also employ antibody libraries from eukaryotic cells that present antibodies on their cell surfaces. More specifically, an expression vector carrying a gene that encodes a desired heavy chain (for example, Fd), and is linked downstream of a promoter appropriate for its expression and a signal sequence which enables the secretion of the heavy chain, is introduced into eukaryotic host cells. Furthermore, expression vectors are constructed with light chain-encoding

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genes linked to a transmembrane region-encoding sequence and inserted downstream of an appropriate promoter, so that the light chains will be displayed on cell surfaces when expressed. The transmembrane region is preferably added to the C terminus of expressed light chains. By introducing light chain expression vectors into the aforementioned heavy chain-secreting host cells, host cells which express on their cell surfaces antibodies that bind to a desired antigen can be selected. The displayed antibody is a Fab fragment when Fd is used as the heavy chain and those comprising VL and CL are used as the light chains.”

The specification does not teach a vector encoding a secretion signal linked to the Fd to be used in combination with a vector encoding the light chain, a bacterial signal sequence and a phage membrane anchor where both are to be used for secretion in prokaryotic cells. This above recited paragraphs and the figures are the extent of written support and enablement for the instant claimed method. Nevertheless, Applicants allege to be usable and enabled combining the elements of i) the first Fd linked to any bacterial secretion signal peptide, ii) the light chains linked to any bacterial secretion signal peptide, and iii) the light chains being further linked to any phage membrane anchor domain and in any order with respect the given Fd and light chain. The examiner does not identify support for the combination of these elements in the manner recited in the claims in the specification or the drawings as filed.

The rejection is maintained.



**New Grounds for Objection**

***Claim Objections***

9. Claims 1, 2, 6, and 7 are objected to because of the following informalities:

a) Each of the claims recites “linked to a bacterial secretion signal” and for purposes of consistency, should seemingly recite “linked to a bacterial secretion signal peptide”. Appropriate correction is required.

***Conclusion***

10. No claims are allowed.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

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12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883.

The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Lynn A. Bristol/  
Primary Examiner, Art Unit 1643